Leukemia Mortality by Cell Type in Petroleum Workers with Potential Exposure to Benzene

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Workers in the petroleum industry are potentially exposed to a variety of petrochemicals, including benzene or benzene-containing liquids. Although a large number of studies of petroleum workers have been conducted to examine leukemia and other cancer risks, few existing studies have investigated cell-type-specific leukemias. One of the major reasons for the lack of cell-type-specific analysis was the small number of deaths by cell type in individual studies. In the present investigation, all cohort studies of petroleum workers in the United States and the United Kingdom were combined into a single database for cell-type-specific leukemia analysis. The majority of these workers were petroleum refinery employees, but production, pipeline, and distribution workers in the petroleum industry were also included. The combined cohort consisted of more than 208,000 petroleum workers, who contributed more than 4.6 million person-years of observation. Based on a meta-analysis of the combined data, cell-type-specific leukemia risks were expressed in terms of standardized mortality ratios (meta-SMRs). The meta-SMR for acute myeloid leukemia was 0.96. The lack of an increase of acute myeloid leukemia was attributed to the low levels of benzene exposure in the petroleum industry, particularly in comparison to benzene exposure levels in some previous studies of workers in other industries, who had been found to experience an increased risk of acute myeloid leukemia. Similarly, no increase in chronic myeloid, acute lymphocytic, or chronic lymphocytic leukemias was found in petroleum workers (meta-SMRs of 0.89, 1.16, and 0.84, respectively). Stratified meta-analyses restricted to refinery studies or to studies with at least 15 years of follow-up yielded similar results. The findings of the present investigation are consistent with those from several recent case–control studies of cell-type-specific leukemia. Patterns and levels of benzene exposure in the petroleum industry are reviewed. The results of the present epidemiologic investigation are discussed in conjunction with recent advances in leukemogenesis from other scientific disciplines. — Environ Health Perspect 104(Suppl 6):1381–1392 (1996)

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Introduction

Exposures to hydrocarbons in the petroleum industry include inhalation of vapors and dermal contact of crude oil, feed stocks, intermediate products during refining, and end products, such as gasoline (*1,2*). Of special concern is benzene, which has been linked to an increased risk of leukemia, particularly acute myeloid leukemia (AML). Case reports suggesting an association between exposure to benzene and leukemia came primarily from England, Italy, France, and Turkey (*3–9*). Documentation, if any at all, of exposures to benzene or benzene-containing mixtures in these case reports was extremely poor. Furthermore, these reports lacked information concerning the size of population at risk, and, therefore, no risk estimates could be derived. Thus, case reports by themselves do not provide definitive evidence for causation, but rather suggest potential areas for future epidemiologic research. One observation, however, emerged from these case reports: the predominant cell type of the reported leukemia cases was AML.

It was not until the 1970s that epidemiologic studies of individuals exposed to benzene were carried out. Judging by today's standards, some of the early studies were rather crude. For example, in the Thorpe (*10*) study of leukemia incidence among employees at eight Esso petroleum affiliates in Europe, only active employees and annuitants, but not separated employees, were included. Furthermore, person-years of observation were estimated and not actually calculated. Similarly, in the Infante et al. (*11*) study of rubber hydrochloride workers exposed to benzene at two Pliofilm manufacturing plants in Ohio, the cohort was incomplete (an unknown number of employment records were missing and no maintenance workers were included). Furthermore, mortality ascertainment in the Infante et al. (*11*) study was only 75% complete. Likewise, employment histories were also incomplete. It appeared that some individuals included in the study had worked at the facilities for only a few days, and some might not have worked there at all (*12*). Subsequent updates of the Infante et al. (*11*) study by others (*13,14*) have improved mortality ascertainment, but the cohort incompleteness remained a major limitation of the study.

In a 1983 report, Wong (*15*) discussed some of the unresolved issues regarding the relationship between benzene and leukemia. The same issues were iterated by a group of scientists convened by the International Agency for Research on Cancer (*16*). One of the major issues raised by both Wong (*15*) and McMichael (*16*) is the relationship, if any, between benzene exposure and leukemia cell types other than AML.

In the past, leukemia was considered a single statistical category in most occupational epidemiologic studies, partly because of the historical nomenclature, unavailability of cell-type-specific rates for comparison, and, most importantly, the paucity of cases by cell type in individual studies (*17,18*). Recently, epidemiologic studies have demonstrated the importance of cell-type-specific analysis in studying leukemia. It has now been recognized that the diseases collectively known as leukemia are several distinct malignancies with different etiologic factors (*19,20*). Similarly, the diversity of different types of

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Abbreviations used: AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; ANLL, acute nonlymphocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic lymphocytic leukemia; PMR, proportional mortality ratio; SMR, standardized mortality ratio.

leukemia has long been recognized by hematologists (*21*).

The need to analyze leukemia data by cell-type in relation to occupational exposures such as benzene has created some interesting challenges to epidemiologists. Workers in the petroleum industry represent one of the largest populations exposed to benzene. Numerous studies based on petroleum workers have been conducted in the United States and in the United Kingdom. Even though most of these studies consist of several thousand workers who have been observed over several decades, few individual studies offer adequate data for cell-type-specific analysis. The objective of the present investigation was to combine all the studies of petroleum workers in the United States and in the United Kingdom into a single large database, which can then be analyzed to evaluate cell-type-specific leukemia risks in these petroleum workers.

Methods and Materials

Based on a consideration of both study design and data quality, only cohort studies were included in the analysis. Studies based on proportional mortality ratios (PMRs) were excluded from analysis because of the following limitations. In addition to the well-known methodological deficiencies of PMR studies (*22,23*), some of the PMR studies of petroleum workers also suffered from incomplete ascertainment of deaths (*24–27*). Furthermore, employment histories were not available in these PMR studies, and analyses were limited. Finally, the petroleum refineries included in these PMR studies have subsequently been studied more thoroughly with the cohort study design.

In addition to cohort and PMR studies, there were also a number of community-based case–control studies of cell-type-specific leukemias, which included petroleum or petroleum-related occupations in the analyses. Most of these studies did not provide adequate information about the nature of exposure or details of employment. Methodological problems (such as control selection, recall of employment histories, adjustment of confounding factors) further complicated the interpretation. Therefore, case–control studies were not included in the quantitative analysis, but formed part of the basis of discussion.

A couple of reports based on linkage between tumor registry and census data have also been published (*28,29*). The Olsen and Jensen (*28*) survey reported a deficit of acute leukemia in men employed at gasoline stations in Denmark, whereas the Jakobsson et al. (*29*) survey reported an increased risk of AML in petrol station attendants in Finland. Both surveys were judged to be inadequate. Using occupational information derived from census data as a surrogate for exposure to specific chemicals can introduce substantial misclassification. Moreover, estimating person-years at risk or expected leukemia cases in certain industries based on census data involves a potentially substantial amount of inaccuracy. The problem of multiple comparisons based on the large number of cancer sites and industries or occupations examined further weakens the statistical findings from these surveys. As such, these reports are inadequate in assessing leukemia risk due to exposure to specific chemicals.

In the present investigation, a meta-analysis procedure was used in combining data from individual cohort studies of petroleum workers. The methodological details of the meta-analysis have been described elsewhere (*30*). Data needed to carry out the meta-analysis included observed leukemia deaths by cell type and the distribution of age-specific person-years from each individual study. These data were usually not presented in published reports. Instead, such data were requested from the original investigators. For some studies, multiple reports on various portions of the cohort and/or updates were available. For the present analysis, data for the entire cohort based on the latest available update were used.

A specific analysis was carried out for each of the four major leukemia cell types [AML or chronic myeloid leukemia (CML), and acute (ALL) or chronic lymphocytic leukemia (CLL)]. The *8th Revision of the International Classification of Diseases* was used in classifying deaths. The codes for AML, CML, ALL, and CLL are 205.0, 205.1, 204.0, and 204.1, respectively. For comparison in the U.S. studies, age-specific mortality rates for each of the four major leukemia cell types were derived from data provided by the National Center for Health Statistics (*31*). Although, in general, the accuracy of diagnosis of leukemia cell types based on death certificates was not as desirable as that based on pathological reports (particularly in the 1940s or 1950s), no potential bias was introduced in the present investigation, since diagnostic information in both petroleum workers and the comparison group (general population) was based on death certificates. Furthermore, the majority of leukemia deaths in petroleum workers occurred in or after the 1960s.

For each U.S. cohort, expected deaths by cell-type were calculated by applying U.S. specific rates to person-years. For the U.K. industry-wide studies, cell-type-specific information has been published, and such information was taken directly from the publications (*32–34*). One Canadian cohort study (*35*) and one Australian prospective survey (*36,37*) were not included in the analysis because cell-type-specific leukemia rates for Canada or Australia were not available.

The statistical procedure for meta-analysis consists of summing the observed and expected deaths for a specific leukemia cell type from individual studies and calculating the summary or meta-standardized mortality ratio (SMR). This simple procedure treats each individual cohort as a separate meta-stratum in data summarization, thus adjusting for individual studies while preserving the original adjustment using substrata specific to age, sex, race, and time period. In the present investigation, both cell-type-specific leukemia meta-SMRs and their corresponding 95% confidence intervals were calculated. Although other statistical procedures for meta-analysis are available, the meta-SMR procedure was used in this investigation because of its simplicity in computation and interpretation, its preservation of the adjustments in the individual studies, and its resemblance to the analyses in the original studies. Similar procedures have been used previously in analyzing data on asbestos and gastrointestinal cancer (*38*), artificial sweeteners and bladder cancer (*39*), formaldehyde and respiratory cancer (*40*), chemical dyes and bladder cancer (*41*), and radiation and colon cancer (*42*). In particular, this method was discussed in the interpretation of negative epidemiological evidence for carcinogenicity by the International Agency for Research on Cancer (*43*).

An additional benefit of meta-analysis is that it takes into consideration the multiple-comparison problem exhibited in the individual cohort studies. As discussed below, a total of 19 individual cohorts have been included in the database, which means there would be 76 (19×4) cell-type-specific SMRs. Approximately four statistically significant SMRs can be expected to occur simply by chance alone at the $\alpha = 5\%$ significance level. By combining data from these 19 cohorts, excesses or deficits due to chance for a particular cell type are less likely to occur. For further discussion on

the meta-analysis of cohort studies, see Wong and Raabe (*30,44*).

Results

Included in the analysis were studies conducted or sponsored by seven major petroleum companies in the United States. Most of these studies consisted of refinery workers (*45–68*), except one, which was based on workers in the production and pipeline division (*69*). A study sponsored by the American Petroleum Institute that consisted of a cohort of land-based petroleum distribution workers and a cohort of marine petroleum distribution workers was also included (*70,71*). From the United Kingdom, two cohort studies of petroleum refinery and distribution workers sponsored by the Institute of Petroleum were included (*32–34,72,73*).

Previously, Wong and Raabe (*30*) provided a meta-analysis of leukemia (all cell types combined) based on studies of petroleum workers available at the time. The total leukemia meta-SMR was 1.12 (not significant) based on 279 deaths. Of the 14 U.S. or U.K. studies reviewed by Wong and Raabe (*30*), 3 refineries (Beaumont, Deer Park, and Woodriver) showed a significant increase in total leukemia. Since the Wong and Raabe (*30*) review, all but two studies in the United States and in the United Kingdom have been updated. In particular, based on the updated data, the total leukemia SMR for the Beaumont refinery has been reduced from 1.73 ($p < 0.05$) to 1.39 ($p > 0.05$), for the Deer Park refinery from 2.31 ($p < 0.05$) to 0.96 ($p > 0.05$), and for the Woodriver refinery from 2.12 ($p < 0.05$) to 1.23 ($p > 0.05$). Thus, all three significantly elevated leukemia SMRs reported in the 1989 review are no longer statistically significant. Furthermore, the updated Amoco study of 10 U.S. refineries showed a significantly low total leukemia SMR of 0.39. Three new cohorts have been included in the present investigation, and the total leukemia SMRs for all three cohorts were < 1.0 (*62,70,71*). The updated total leukemia meta-SMR based on all petroleum cohorts in the United States and the United Kingdom has been recalculated to be 1.02 (498 observed deaths, 95% CI: 0.93–1.11).

Table 1 provides a basic description of the individual U.S. and U.K. cohort studies included in the present investigation. Although exposure patterns in each cohort might differ, all workers were potentially exposed to benzene-containing petroleum liquids as well as other hydrocarbons. It is quite likely that the within-cohort exposure variation is comparable to, if not greater than, the between-cohort exposure variation.

In the present investigation, a total of 19 individual cohorts were included in the meta-analyses. The combined cohort consisted of more than 208,000 petroleum workers, with approximately 150,000 from the United States and 58,000 from the United Kingdom. Over an observation period of 53 years (1937–1989), these workers contributed more than 4.6 million person-years. More than 56 thousand deaths were reported in these studies. In particular, 498 deaths were ascribed to leukemia. Based on information available, 327 (66%) leukemia deaths among the petroleum workers were classifiable into one of the four major cell types: AML, CML, ALL, and CLL. Thus, 34% leukemia deaths in petroleum workers belonged to other or unspecified cell types. According to data provided by the National Center for Health Statistics (*74*), the corresponding figure in the general population was similar (32–34%).

The distributions of leukemia deaths among the U.S. and the U.K. petroleum workers by the four major cell-types were similar (Table 2). The cell-type distribution for the U.S. and U.K. combined cohort of petroleum workers was also similar to that in the general adult population (age 15 or older), which was derived from Selvin et al. (*31*). A formal goodness-of-fit test between the U.S. and U.K. combined cohort of petroleum workers and the general population indicated that there was no significant difference between the two distributions ($\chi^2 = 2.00$, 3df, $p = 0.57$).

Table 3 and Figure 1 present the results of AML analysis for individual cohorts as well as for the combined cohorts. Because

Table 1. Description of epidemiologic study cohorts in the petroleum industry in the United States and the United Kingdom.

Organization	Cohort location	Number of workers	Observation period	Person-years	Total deaths	References
Amoco	10 refineries in U.S.	10,763	1970–1986	125,241	1,405	Hornstra (*45*); Nelson (*46*)
Chevron	El Segundo, CA, refinery	4,773	1950–1986	110,594	1,121	Dagg et al. (*47*); Wong et al. (*48*)
	Richmond, CA, refinery	8,523	1950–1986	205,397	2,038	
Chevron (Gulf)	Port Arthur, TX, refinery	17,844	1937–1987	526,386	6,799	Satin et al. (*49*); Wen et al. (*50*)
Exxon	Baton Rouge, LA, refinery	9,894	1970–1982	93,785	2,000	Shallenberger et al. (*51*); Hanis et al. (*52–54*)
	Baytown, TX, refinery	8,722	1970–1982	80,684	1,374	
	Bayway, NJ, refinery	6,860	1970–1982	59,257	1,826	
Mobil	Beaumont, TX, refinery	7,119	1945–1987	166,427	2,294	Raabe et al. (*55*); Milcarek et al. (*56*); Collingwood et al. (*57*); Morgan and Wong, (*58,59*); Enterline et al. (*60*)
	Paulsboro, NJ, refinery	4,855	1946–1987	120,718	1,681	
	Torrance, CA, refinery	1,991	1959–1987	33,331	408	
Shell	2 California refineries	4,585	1973–1989	57,657	1,051	Tsai et al. (*62*); Marsh et al. (*61*); Honda et al. (*63*); Wongsrichanalai et al. (*64*); McCraw et al. (*65*); Joyner (*66*)
	Deer Park, TX, refinery	6,831	1948–1983	181,782	1,180	
	Woodriver, IL, refinery	9,796	1940–1989	300,991	3,627	
Texaco	13 refineries in U.S.	19,077	1947–1977	358,318	4,024	Divine et al. (*67*); Divine and Barron (*68,69*)
	Production and pipeline in U.S.	11,098	1946–1980	220,414	1,886	
American Petroleum Institute	Land-based terminals in U.S.	9,026	1946–1989	239,125	2,066	Wong et al. (*71*); Wong and Trent (*70*)
	Marine vessels in U.S.	9,109	1946–1989	227,143	2,695	
Institute of Petroleum	8 refineries in U.K.	34,569	1951–1989	931,640	10,193	Rushton (*32–34*); Rushton and Alderson (*72,73*)
	Distribution centers in U.K.	23,306	1951–1989	626,471	8,743	
Total	U.S. and U.K. petroleum workers	208,741	1937–1989	4,665,361	56,411	

Table 2. Comparison of leukemia cell-type distribution between petroleum workers and the general population.[a]

Cell type	No. of petroleum workers (%)			General population, %
	U.S. (%)	U.K. (%)	U.S.–U.K. (%)	
Acute myeloid leukemia	103 (46)	45 (45)	148 (46)	43
Chronic myeloid leukemia	43 (19)	19 (19)	62 (19)	19
Acute lymphocytic leukemia	25 (11)	9 (9)	34 (10)	11
Chronic lymphocytic leukemia	55 (24)	28 (28)	83 (25)	28
Total	226 (100)	101 (100)	327 (100)	100

[a]Goodness-of-fit test between the U.S. and U.K. combined cohort of petroleum workers and the general population, $\chi^2 = 2.00$, 3df, $p = 0.57$.

Table 3. Meta-analysis of acute myeloid leukemia in petroleum workers in the United States and the United Kingdom, 1937 to 1989.

Country	Cohort	Observed deaths	Expected deaths	SMR	95% CI
U.S.	A	3	4.87	0.62	0.13–1.81
	B	6	6.33	0.95	0.35–2.07
	C	6	4.48	1.34	0.49–2.92
	D	0	3.37	0	0–1.09
	E	4	4.45	0.90	0.24–2.30
	F	4	2.80	1.43	0.39–3.66
	G	14	10.90	1.28	0.70–2.15
	H	7	6.91	1.01	0.41–2.08
	I	5	7.88	0.63	0.20–1.47
	J	6	3.56	1.69	0.62–3.68
	K	10	15.95	0.63	0.30–1.16
	L	4	3.65	1.10	0.30–2.82
	M	8	6.15	1.30	0.56–2.56
	N	0	1.23	0	0–3.00
	O	1	4.23	0.24	0.01–1.34
	P	12	12.11	0.99	0.51–1.73
	Q	13	8.81	1.48	0.79–2.53
U.S. combined cohort		103	107.68	0.96	0.78–1.16
U.K.	R	20	26.60	0.75	0.45–1.15
	S	25	20.60	1.21	0.78–1.79
U.K. combined cohort		45	47.20	0.95	0.70–1.27
U.S.–U.K. combined cohort		148	154.88	0.96	0.81–1.13

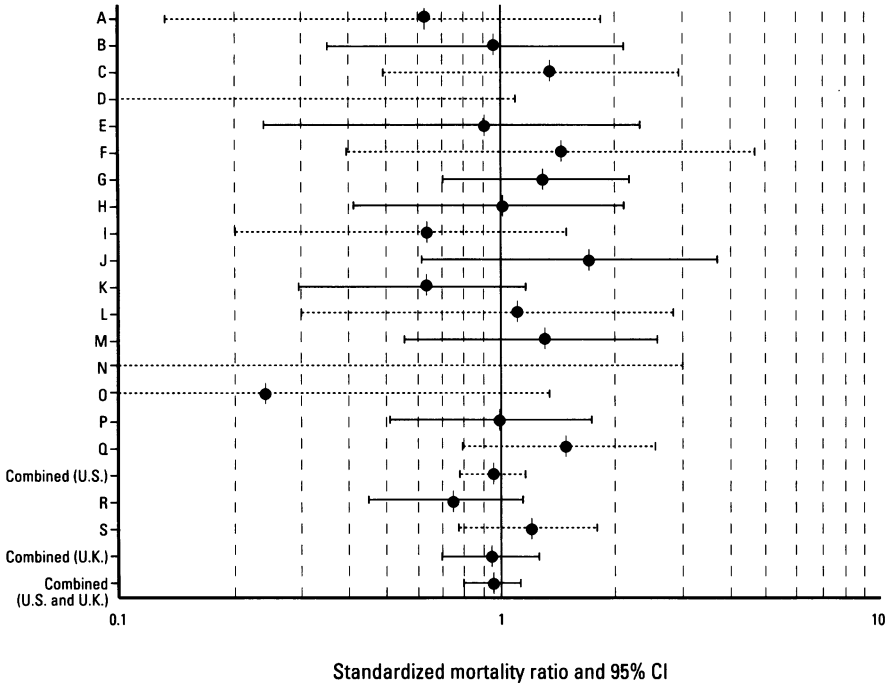

Figure 1. Acute myeloid leukemia among petroleum workers in the U.S. and the U.K., 1937–1989; 148 observed deaths, meta-standardized mortality ratio = 0.96 (95% CI: 0.81–1.13).

of the logarithmic scale, for SMRs < 0.1, neither the point estimate nor the lower 95% confidence limit is presented in the figure. The number of observed AML deaths in each cohort ranged from 0 to 25. No significantly elevated AML SMR was detected for any cohort. For cohort D, no AML deaths were observed, and, based on 3.37 expected, this deficit was almost statistically significant (SMR = 0, 95% CI: 0–1.09, $p = 0.06$). For the U.S. combined cohort, 103 AML deaths were reported, compared to 107.68 expected. The corresponding AML meta-SMR for the U.S. combined cohort was 0.96, with a 95% CI of 0.78 to 1.16. The U.K. combined cohort yielded similar results for AML (meta-SMR = 0.95, 95% CI: 0.70–1.27). For the U.S.–U.K. combined cohort, there were 148 observed AML deaths, which were comparable to the 154.88 expected, and the meta-SMR for AML was 0.96 (95% CI: 0.81–1.13).

Results based on a similar analysis for CML are shown in Table 4 and in Figure 2. In the United States, most cohorts contributed fewer than five CML deaths each, and the highest number of eight observed CML deaths was reported in cohort P. No significant CML SMR was found in any of the individual cohorts. For the U.S. combined cohort, 43 observed deaths were ascribed to CML, whereas 47.97 CML deaths were expected. For the U.S. combined cohort, the CML meta-SMR was 0.90, and the 95% CI was 0.65 to 1.21. For the U.K. combined cohort, the meta-SMR for CML was 0.86 (19 observed versus 22.00 expected, 95% CI: 0.52 to 1.35). For the U.S. and U.K. combined cohort, a total of 62 CML deaths were observed, compared to 69.97 expected. The CML meta-SMR for all petroleum workers was 0.89 (95% CI: 0.68–1.15).

ALL accounted for only 10 to 11% of the four major cell types combined in both the petroleum workers and in the general population (Table 2). The number of ALL deaths in each individual study was extremely small. No more than two ALL deaths were reported in most cohorts, and six cohorts reported no ALL deaths at all (Table 5, Figure 3). In cohort K, however, 8 ALL deaths were observed, compared to 3.08 expected. The ALL SMR for cohort K was 2.60 (95% CI: 1.12–5.11). No other cohort reported a significant ALL SMR. In the U.S. combined cohort, 25 ALL deaths were reported, slightly higher than the 20.26 expected. The ALL meta-SMR for the U.S. combined cohort was 1.23, which

Table 4. Meta-analysis of chronic myeloid leukemia in petroleum workers in the United States and the United Kingdom, 1937 to 1989.

Country	Cohort	Observed deaths	Expected deaths	SMR	95% CI
U.S.	A	0	2.06	0	0–1.79
	B	2	2.85	0.70	0.08–2.53
	C	3	1.97	1.52	0.31–4.44
	D	2	1.55	1.29	0.16–4.66
	E	1	1.98	0.51	0.01–2.84
	F	0	1.26	0	0–2.93
	G	2	4.85	0.41	0.05–1.48
	H	3	3.08	0.97	0.20–2.83
	I	4	3.52	1.14	0.31–2.92
	J	1	1.60	0.62	0.02–3.45
	K	6	7.11	0.84	0.31–1.83
	L	4	1.58	2.53	0.69–6.48
	M	3	2.74	1.09	0.22–3.18
	N	2	0.54	3.68	0.54–13.28
	O	1	1.92	0.52	0.01–2.90
	P	8	5.40	1.48	0.64–2.92
	Q	1	3.95	0.25	0.01–1.39
U.S. combined cohort		43	47.97	0.90	0.65–1.21
U.K.	R	11	12.30	0.89	0.44–1.59
	S	8	9.70	0.82	0.35–1.62
U.K. combined cohort		19	22.00	0.86	0.52–1.35
U.S.–U.K. combined cohort		62	69.97	0.89	0.68–1.15

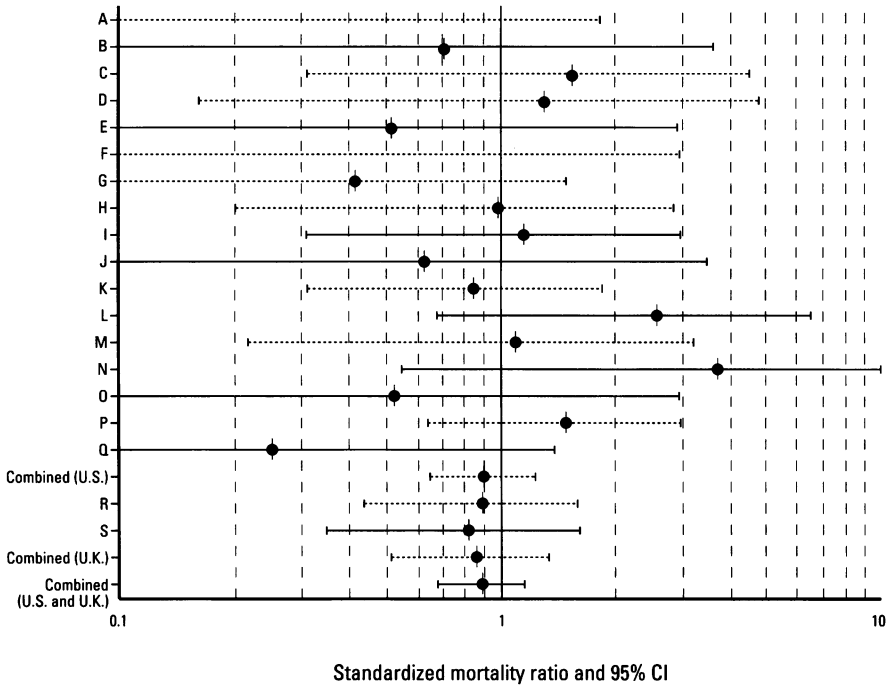

Figure 2. Chronic myeloid leukemia among petroleum workers in the U.S. and the U.K., 1937–1989; 62 observed deaths, meta-standardized mortality ratio = 0.89 (95% CI: 0.68–1.15).

was not significant (95% CI: 0.79–1.81). The ALL meta-SMR for the U.K. combined cohort was slightly less (meta-SMR = 0.99, 95% CI: 0.45–1.88). In the overall combined cohort of both U.S. and U.K. petroleum workers, the observed number of ALL deaths was 34, whereas the expected number was 29.36; and the ALL meta-SMR was 1.16 (95% CI: 0.81–1.61).

Table 6 and Figure 4 present the results of the CLL analysis. In the United States, most individual cohorts reported four or fewer CLL deaths. Of the 17 U.S. cohorts, 13 reported a lower than expected CLL mortality. In fact, cohort K reported a significantly low CLL SMR of 0.30 (3 observed versus 10.04 expected, 95% CI: 0.06–0.87). On the other hand, cohort C reported a significantly high CLL SMR of 2.59 (9 observed vs 3.48 expected, 95% CI: 1.18–4.91). A total of 55 CLL deaths were observed in the U.S. combined cohort, almost significantly less than the 69.19 expected (meta-SMR = 0.79, 95% CI: 0.59–1.03). There were 28 observed CLL deaths in the U.K. combined cohort, slightly less than the 29.70 expected (meta-SMR = 0.94, 95% CI: 0.63–1.36). In the U.S. and U.K. combined cohort, 83 CLL deaths were observed, whereas 98.89 were expected; and the CLL meta-SMR was 0.84 (95% CI: 0.67–1.04).

The above meta-analyses were based on all 19 cohorts of petroleum workers; including refinery, production and pipeline, and distribution workers. If the meta-analyses were restricted to the 15 refinery cohorts (14 from the United States and 1 from the United Kingdom), the cell-type-specific leukemia results remained essentially unchanged. The meta-SMRs for petroleum refinery workers in the United States and in the United Kingdom were 0.93, 0.94, 1.32, and 0.87 for AML, CML, ALL, and CLL, respectively (Table 7). None of the meta-SMRs for the U.S.–U.K. combined cohort of petroleum refinery workers was statistically significant.

Among the 19 cohorts included in the analysis, length of follow-up ranged from 13 to 51 years. A separate analysis was carried out based on cohorts with at least 15 years of follow-up. Using this criterion, three cohorts were excluded. The results of this analysis based on cohorts with 15+ years of follow-up are presented in Table 8. The results for follow-up of 15+ years remained essentially the same.

Discussion

The combined database in the meta-analysis represented one of the largest databases in epidemiologic research. Even though most of the individual cohorts were relatively large, it is evident from Tables 3–6 that most of the cell-type-specific leukemia SMRs based on individual cohorts were unstable, as most were based on small numbers of deaths (particularly for ALL). One of the major advantages of the meta-analyses carried out in the present investigation is the stability of the combined data.

With regard to cell-type-specific leukemia analyses, the statistical power of the individual cohorts was limited. This

was particularly true for the U.S. cohorts, most of which were individual company or individual refinery studies. The two U.K. studies were larger, because they were industry-wide studies consisting of workers from several companies. Based on the average of the 17 individual cohorts in the United States, the minimum SMR detectable at $\alpha = 0.05$ and $\beta = 0.20$ in an individual cohort were 2.22, 3.02, 4.57, and 2.61 for AML, CML, ALL, and CLL, respectively. All of these SMRs were higher than 2-fold. The inadequacy of statistical power of individual studies was particularly evident for ALL.

Statistical power increased substantially by combining the 17 U.S. cohorts. Table 9 presents the minimum detectable SMRs at $\alpha = 0.05$ and $\beta = 0.20$ for each of the four major cell types. For AML, the U.S. combined cohort provides sufficient statistical power (80% power at the 0.05 level) to detect a risk ratio as small as 1.25, if indeed there was an increased risk. Based on the U.S. combined cohort, the minimum detectable SMRs were 1.39 for CML and 1.32 for CLL, respectively. Even for ALL, the least frequent cell type, the minimum detectable SMR based on the U.S. combined cohort was 1.63. All the minimum detectable SMRs based on the U.S. combined cohort were less than 2-fold. The statistical power of the U.K. combined cohort was somewhat lower (Table 9). In the overall U.S. and U.K. combined cohort of petroleum workers, the minimum detectable SMRs were 1.21, 1.32, 1.51, and 1.26 for AML, CML, ALL, and CLL, respectively. Thus, the absence of an increased risk of AML, CML, ALL, or CLL in petroleum workers in the United States or in the United Kingdom based on the meta-analyses in the present investigation could not be attributed to inadequate statistical power.

One may question why an increased risk of AML was not observed in petroleum workers, who were certainly exposed to some levels of benzene. The answer probably lies in the threshold of benzene exposure required to produce a significant increase of AML. To estimate the threshold, the data from the study of Pliofilm workers exposed to benzene (*14*) updated through 1987 were analyzed specifically for AML in a recent investigation (*75*). For the Pliofilm cohort as a whole, 6 deaths from AML were observed, compared to 1.19 expected (Table 10). The corresponding AML SMR of 5.03 was statistically significant. However, exposure–response analysis indicated that no increase of AML was detected for cumulative exposure below 200 ppm-years (SMR = 0.91). Furthermore, the exposure levels provided by Rinsky et al. (*14*) were likely underestimated, and more realistic exposure estimates have been developed by others (*76,77*). Had the other exposure estimates been used, the observed AML threshold would have been much higher, most likely in the range of 370 to 530 ppm-years (*75*). Emerging evidence in the biologic search for a mechanism of benzene-induced AML suggests that benzene and its metabolites

Table 5. Meta-analysis of acute lymphocytic leukemia in petroleum workers in the United States and the United Kingdom, 1937 to 1989.

Country	Cohort	Observed deaths	Expected deaths	SMR	95% CI
U.S.	A	0	0.84	0	0–4.39
	B	1	1.22	0.82	0.02–4.57
	C	1	0.89	1.12	0.03–6.24
	D	0	0.70	0	0–5.27
	E	1	0.83	1.20	0.03–6.68
	F	0	0.54	0	0–6.83
	G	3	2.02	1.49	0.31–4.36
	H	1	1.32	0.76	0.02–4.23
	I	1	1.47	0.68	0.02–3.79
	J	2	0.68	2.96	0.36–10.69
	K	8	3.08	2.60*	1.12–5.11
	L	0	0.69	0	0–5.35
	M	0	1.17	0	0–3.15
	N	0	0.23	0	0–16.04
	O	2	0.82	2.45	0.30–8.84
	P	3	2.14	1.40	0.29–4.09
	Q	2	1.62	1.23	0.15–4.44
U.S. combined cohort		25	20.26	1.23	0.79–1.81
U.K.	R	4	5.30	0.75	0.20–1.92
	S	5	3.80	1.32	0.43–3.08
U.K. combined cohort		9	9.10	0.99	0.45–1.88
U.S.–U.K. combined cohort		34	29.36	1.16	0.81–1.61

*$p < 0.05$.

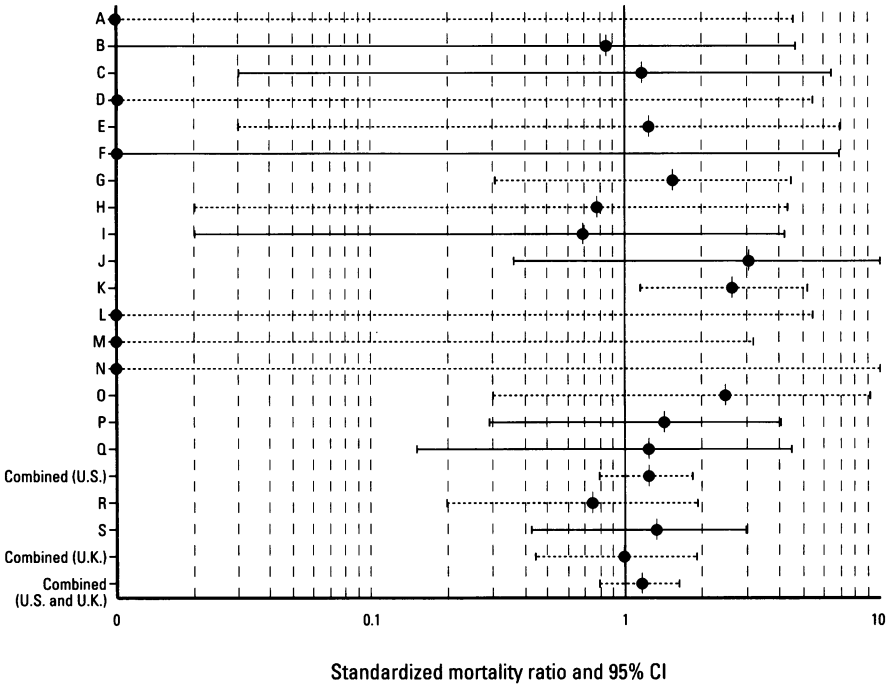

Figure 3. Acute lymphocytic leukemia among petroleum workers in the U.S. and the U.K., 1937–1989; 34 observed deaths, meta-standardized mortality ratio = 1.16 (95% CI: 0.81–1.61).

Table 6. Meta-analysis of chronic lymphocytic leukemia in petroleum workers in the United States and the United Kingdom, 1937 to 1989.

Country	Cohort	Observed deaths	Expected deaths	SMR	95% CI
U.S.	A	2	2.97	0.67	0.08–2.42
	B	5	3.79	1.32	0.43–3.08
	C	9	3.48	2.59*	1.18–4.91
	D	1	3.00	0.33	0.01–1.84
	E	2	2.92	0.69	0.08–2.49
	F	4	2.18	1.84	0.50–4.71
	G	8	6.99	1.14	0.49–2.24
	H	2	4.10	0.49	0.06–1.77
	I	4	4.99	0.80	0.22–2.05
	J	2	2.19	0.91	0.11–3.29
	K	3	10.04	0.30*	0.06–0.87
	L	2	2.67	0.75	0.09–2.71
	M	1	4.09	0.24	0.01–1.34
	N	0	0.79	0	0–4.67
	O	1	1.91	0.52	0.01–2.90
	P	7	7.22	0.97	0.39–2.00
	Q	2	5.87	0.34	0.04–1.23
U.S. combined cohort		55	69.19	0.79	0.59–1.03
U.K.	R	12	15.80	0.76	0.39–1.33
	S	16	13.90	1.15	0.66–1.86
U.K. combined cohort		28	29.70	0.94	0.63–1.36
U.S.–U.K. combined cohort		83	98.89	0.84	0.67–1.04

*$p < 0.05$.

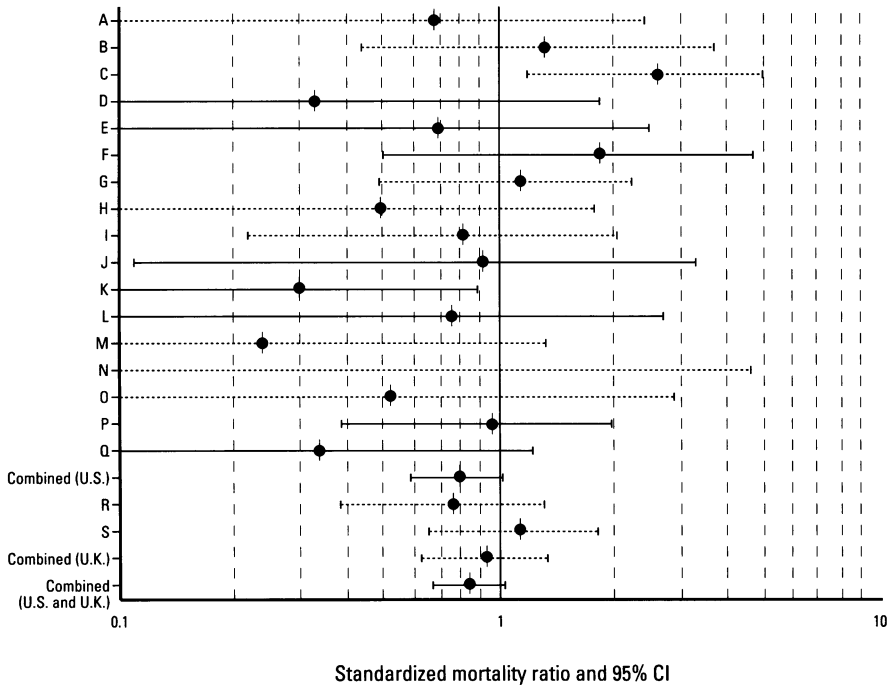

Figure 4. Chronic lymphocytic leukemia among petroleum workers in the U.S. and the U.K., 1937–1989; 83 observed deaths, meta-standardized mortality ratio = 0.84 (95% CI: 0.67–1.04).

may induce AML via toxic disruption of regulatory mechanisms of cell growth and differentiation (*78*). If benzene-induced toxicity is a conditional step in benzene-related AML, this would lend biologic support to the observed threshold based on epidemiologic data (*79*). Thus, the lack of an increased risk of AML in petroleum workers could have been due to the substantially lower benzene exposures in the petroleum industry than in the Pliofilm study, which included workers exposed to benzene levels as high as several hundred parts per million.

Similarly, benzene exposure levels in case reports of AML in shoemakers from Istanbul, Turkey, were extremely high. These shoemakers, who used solvents containing up to 88% benzene, were exposed to air benzene levels up to 650 ppm (*80*). In addition, some of these shoemakers worked at their homes and were thus exposed all day and all week long.

On the contrary, benzene exposure at refineries were substantially lower compared to levels at the Pliofilm plants or among Istanbul shoemakers. For example, for general plant operations at petroleum refineries in the United States, the mean benzene level of 14,824 samples from an industry-wide survey was 0.22 ppm (*1*). For gauging content in the field (by production workers) or at refinery tank farms (by refinery workers), 60% of the industrial hygiene samples were < 1 ppm, 22% between 1 and 5 ppm, 8% between 5 and 10 ppm, 7% between 10 and 25 ppm, and only 2% between 25 and 50 ppm. Similarly, based on a comprehensive survey in the petroleum refining industry, Spears et al. (*81*) reported that most measurements based on both 8-hr and 15-min time-weighted average benzene exposures were below 1 ppm.

For U.S. land-based gasoline distribution workers, the highest exposures were received by drivers of tank trucks using the splash method for loading during 1950 to 1964 (*82*); and their full-shift exposure level for total hydrocarbons was estimated to be 220 ppm, which was equivalent to approximately 3.5 ppm of benzene (*83*). For U.S. marine distribution workers, the highest exposures occurred among deck personnel during loading with open-hatch venting (*82*); and their full-shift exposure level for total hydrocarbons was estimated to be 250 ppm, or approximately 4 ppm of benzene. Because of the higher benzene content in gasoline in the United Kingdom (generally twice as much), benzene exposures in U.K. distribution workers have been and are higher than their U.S. counterpart (perhaps, by a 2-fold difference). These exposure data indicated that petroleum workers, even including those who worked in the industry decades ago, would not have accumulated sufficient benzene exposure in excess of the estimated AML threshold derived from the Pliofilm study.

Distribution of leukemia cases by cell type in the petroleum workers was similar to that in the general adult population (Table 2). In particular, of the four major cell types, AML accounted for 46% in the petroleum workers and 43% in the general

Table 7. Meta-analysis of cell-type specific leukemias in refinery workers in the United States and the United Kingdom, 1937 to 1989.

Cell type	Observed deaths	Expected deaths	Meta-SMR	95% CI
Acute myeloid leukemia	78	84.08	0.93	0.73–1.16
Chronic myeloid leukemia	35	37.42	0.94	0.65–1.31
Acute lymphocytic leukemia	21	15.85	1.32	0.81–2.01
Chronic lymphocytic leukemia	47	54.23	0.87	0.64–1.16

Table 8. Meta-analysis of cell-type-specific leukemias in petroleum workers in the United States and the United Kingdom, 1937 to 1989, based on cohorts with 15 or more years of follow-up.

Cell type	Observed deaths	Expected deaths	Meta-SMR	95% CI
Acute myeloid leukemia	138	143.38	0.96	0.81–1.14
Chronic myeloid leukemia	53	64.86	0.82	0.62–1.08
Acute lymphocytic leukemia	33	27.08	1.22	0.83–1.71
Chronic lymphocytic leukemia	71	89.74	0.79	0.62–1.00

Table 9. Minimum detectable standard mortality ratios (at $\alpha = 0.05$ and $\beta = 0.20$) by leukemia cell type in combined cohorts of petroleum workers.

Combined cohort	Cell type	Observed deaths	Expected deaths	Meta-SMR	95% CI		p-Value	Minimum detectable SMR
					Lower limit	Upper limit		
U.S.	AML	103	107.68	0.96	0.78	1.16	0.65	1.25
	CML	43	47.97	0.90	0.65	1.21	0.47	1.39
	ALL	25	20.26	1.23	0.79	1.81	0.29	1.63
	CLL	55	69.19	0.79	0.59	1.03	0.08	1.32
U.K.	AML	45	47.20	0.95	0.70	1.27	0.75	1.39
	CML	19	22.00	0.86	0.52	1.35	0.51	1.60
	ALL	9	9.10	0.99	0.45	1.88	0.97	1.99
	CML	28	29.70	0.94	0.63	1.36	0.75	1.51
U.S. and U.K.	AML	148	154.88	0.96	0.81	1.13	0.58	1.21
	CML	62	69.97	0.89	0.68	1.15	0.34	1.32
	ALL	34	29.36	1.16	0.81	1.61	0.40	1.51
	CLL	83	98.89	0.84	0.67	1.04	0.10	1.26

Table 10. Acute myeloid leukemia by cumulative benzene exposure.

Cumulative exposure, ppm-years	Observed deaths		Expected deaths		SMR		95% CI	
<40	1	1	0.84	1.09	1.19	0.91	0.03–6.63	0.02–5.11
40–200	0		0.25		0		0–14.75	
200–400	2		0.07		27.21**		3.29–98.24	
400+	3		0.03		98.37**		20.28–287.65	
Total	6		1.19		5.03**		1.84–10.97	

**$p < 0.01$.

adult population. In contrast, 85% of the leukemia patients with benzene exposure in Istanbul (the majority being shoemakers) had acute nonlymphocytic leukemia (ANLL) (*19,84*).

Because of the generally low benzene exposures among petroleum workers, the lack of an increased risk of AML is not surprising. Of the 19 individual cohorts examined, none showed a statistically significant AML SMR. In a previous analysis based on cohort G, AML was significantly elevated (SMR = 2.19, 95% CI: 1.13–3.82) (*64*). A nested case–control study within cohort G has been conducted to determine the cause of the increase (*85*). The investigation did not identify any specific job or department responsible for the increase, and comparison of the benzene exposure levels of cases and controls did not indicate any association with benzene exposure at the refinery. The authors offered several possible reasons for the increase: *a*) unidentified exposures other than benzene at the refinery, *b*) exposures at work sites other than the refinery, *c*) unidentified nonoccupational exposures, or *d*) chance. Based on the present meta-analysis, it was unlikely that some yet unidentified exposures other than benzene were responsible for the AML increase reported in the previous analysis of cohort G, unless these unidentified exposures were unique to that particular refinery. More likely, the AML increase in cohort G was due to one or more of the other three reasons offered by the investigators of the original study. For example, cigarette smoking and other nonoccupational lifestyle risk factors have been linked to an increased risk of AML in some recent studies (*19,86–88*). In any event, the analysis based on the latest update of cohort G indicated that AML was no longer significantly elevated (SMR = 1.28, 95% CI: 0.70–2.15).

For CML, no significant increase or deficit was observed in the individual cohorts of petroleum workers. The meta-analyses based on the combined cohorts showed that there was no increase of CML. This finding of no increased CML risk was further supported by two case–control studies of CML. In a case-control study of CML in Sweden, no association ($p = 0.91$) was found between the disease and occupational exposures to petroleum products (*95*). Thus, the authors concluded that, unlike the patients with ANLL, occupational exposures to petroleum products was not particularly common among the patients with CML (*95*). In another case–control study of CML conducted by investigators at the University of Leeds and the University of Edinburgh (*89*), exposure histories of 122 CML cases and 241 controls were examined. This study did not find any association between CML and exposures to benzene or solvents ($p = 0.41$). The authors concluded that the study failed to reveal any risks for solvent or chemical exposure (*89*). Thus, there is no increased CML risk associated with chronic exposures to benzene or other aromatic hydrocarbons. This conclusion is consistent with the view expressed in the *Ceil Textbook of Medicine* (19th ed., p. 933): "Benzene exposure increases the risk of acute myelogenous leukemia (AML) but not of CML" (*90*).

For ALL, only cohort K showed a significant increase (SMR = 2.60, 95% CI: 1.12–5.11). A review of the available employment histories of the ALL cases by the authors of the original cohort did not shed any additional light on a possible explanation for the excess. Moreover, it is interesting to note that there was a significant deficit of CLL (3 observed vs 10.04 expected) in the same cohort. Five of the eight ALL cases in cohort K were diagnosed in a small county in the South, and,

therefore, the ALL excess coupled with a CLL deficit could have been the result of misclassification due to local diagnostic practice. Even if only one case had been misclassified, the ALL SMR for cohort K would not have been statistically significant.

No other individual cohorts showed a significant increase of ALL. In fact, no ALL deaths were reported in six individual cohorts. For the U.S. and U.K. combined cohort, the observed number of ALL deaths was not significantly different from the expected (34 observed versus 29.36 expected, $p = 0.40$). Because of the rarity of ALL, few population-based case–control studies of ALL have addressed the issue of ALL in petroleum workers. In a case-control study based on 5147 leukemia deaths from 16 states in the United States, Loomis and Savitz (*91*) reported that not a single ALL case had worked in the petroleum refining industry (odds ratio = 0). Although the number of ALL in the study was not reported, it can be estimated that approximately 10% of the total number or 500 were ALL. The finding from the Loomis and Savitz (*91*) study that none of the ALL cases worked in the petroleum industry supported the results of the ALL meta-analysis in the present investigation. In a review on environmental factors of leukemia, Brandt (*92*) also concluded that, unlike ANLL, there is little evidence that the development of ALL is related to exposure to some chemicals.

Finally for CLL, as remarked above, cohort K exhibited a significant deficit. On the other hand, cohort C showed a significant excess of CLL (SMR = 2.59, 95% CI: 1.18–4.91). As discussed earlier, approximately 4 statistically significant SMRs could be expected to occur by chance, given that there were 76 SMRs tested at the $\alpha = 0.05$ level. Indeed, there were three statistically significant SMRs in Tables 3 to 6. For the U.S. combined cohort, the CLL SMR was 0.79 (95% CI: 0.59–1.03), almost significantly low at the 0.05 level. For the U.S. and U.K. combined cohort, the CLL meta-SMR was 0.84, indicating that there was no increased CLL risk among petroleum workers in the United States or the United Kingdom. This finding was supported by a recent case–control study of chronic lymphocytic leukemia and chemical exposures conducted by epidemiologists at the University of Washington (*93*). This study found that the risk ratio for CLL associated with exposure to aromatic hydrocarbons (including benzene) was 1.1. Similarly, in a case-control studies of 342 CLL cases in the Baltimore area, benzene was found to be unrelated to any increased risk of CLL (*94*). In the case–control study conducted by Loomis and Savitz (*91*) discussed above, no significant increase in CLL among petroleum refining workers was found. Similarly, in the Swedish case-control study conducted by Brandt et al. (*95*) discussed earlier, no association between exposure to petroleum products and CLL was detected ($p = 0.70$).

In addition to the overall meta-analyses based on all cohort studies of petroleum workers in the United States and the United Kingdom, we also conducted meta-analyses restricted to studies of refinery workers only (Table 7). The results-based refinery studies were similar to those based on all petroleum studies. Furthermore, we also performed meta-analyses based on studies with at least 15 years of follow-up (Table 8). The results remained unchanged, after stratification by length of follow-up.

As discussed previously (*30,44*), data are not available from individual studies for a meta-analysis by level of exposure to petroleum products. A few individual studies have presented exposure–response analyses by leukemia cell type. A review of these analyses will shed additional light on the interpretation of the meta-analyses in the present investigation. For refinery workers, in the case–control study of cohort G, detailed analyses of AML by benzene exposure categories were carried out (*85*). The controls were found to have a higher cumulative benzene exposure than the AML cases. Other cumulative measures of benzene exposure were obtained using different weighting schemes, and for each of these measures the controls consistently scored higher than the cases. Thus, the AML increase reported in the previous analysis of cohort G could not be attributed to benzene exposure. Furthermore, the increase was substantially reduced and no longer statistically significant in the latest update of cohort G.

Among petroleum distribution workers, drivers of tank trucks have the highest potential for exposure to hydrocarbons including benzene. In the U.K. distribution study, Rushton (*34*) provided cell-type-specific analysis for drivers. The AML SMR for drivers was 1.55 (95% CI: 0.82–2.65). Unfortunately, no analysis by exposure to either total hydrocarbons or benzene was carried out. Analysis by hire date indicated that an increased leukemia risk (all cell types) was observed in workers who started work before 1940, but it was not clear whether this result holds true for AML as well. In the U.S. study of distribution workers, no increased risk for either leukemia (all cell-types combined) or AML was found for drivers. Furthermore, exposure-response analyses were carried out for both leukemia (all cell-types combined) and AML in the U.S. study (*70,71*). Analyses using logistic regression models based on length of exposure, cumulative exposure, and frequency of peak exposure did not find any increased risk or exposure–response relationship between these exposure indices and leukemia (all cell-types combined) or AML (*70*). Thus, these detailed analyses from individual studies supported the results of the meta-analyses based on the combined cohorts in the present investigation.

Conclusion

Epidemiologic data have demonstrated that, given high enough exposure levels over an extended period of time, benzene can increase the risk of AML. Furthermore, where quantitative exposure estimates are available, epidemiologic data have indicated that the observed threshold needed to increase the risk of AML has been estimated to be at least 200 ppm-years of benzene exposure, and most likely substantially higher based on more realistic exposure estimates (in the range of 370–530 ppm-years). The meta-analysis on AML in the present investigation based on a combined cohort of more than 208,000 U.S. and U.K. petroleum workers has demonstrated that these workers were not at an increased risk of AML because benzene exposure levels in the petroleum industry have been substantially lower than needed to reach the observed threshold.

Furthermore, in assessing the relationship between benzene exposure and leukemia, a distinction must be made with respect to histological cell types of leukemia. The meta-analyses on CML, A, and CLL have demonstrated that there is no increased risk for any of these cell-type-specific leukemias among petroleum (refinery, production, pipeline, and distribution) workers in the United States or in the United Kingdom. Meta-analyses restricted to refinery studies or to studies with at least 15 years of follow-up yielded similar results. The conclusion of the present investigation is supported by case–control studies on cell-type-specific leukemias conducted in the United States, the United Kingdom, and other countries.

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